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ORIGINAL ARTICLE

Spectrum of Presentation of Vitamin B_{12} Deficiency in Adult Patients in a Tertiary Care Hospital

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ABSTRACT

Background: Severe Vitamin B12 deficiency has a fatal outcome. There are various manifestations of the disease but not many studies of the deficiency have been carried out in India.Most of these studies are laboratory based and not clinician based. There is a need to delve into the spectrum of presentations to enhance clinician suspicion towards the deficiency and supplement patients with Vitamin B12 to reduce the symptomatology.

Objective: **Primary -** To elicit the spectrum of manifestations of the Vitamin B12 deficiency in an adult population in a tertiary hospital.

Secondary - To correlate demographic data including age, gender, socio-economic data and to study hematological, neurological and other complications.

Methods: A descriptive cross sectional study from May, 2014 to May, 2015 in Max Super Specialty Hospital, Saket, New Delhi based on laboratory values of serum Vitamin B12 <145 pg/ml and borderline <180 pg/ml requested by physicians on their clinical suspicion of vitamin B12 deficiency in 100 patients.

Results: Vitamin B12 deficiency was found in age group more than 60 years of age (15%) with not much gender preference (males 52% and females 48%).In this study of Vitamin B12 deficient patients, 2% subjects were lactose intolerant. 77% took milk products however, 21% did not take any milk products; 14% of the people took alcohol, 8% were occasional drinkers and 2 % quit drinking, 76% of the people did not drink at all; 9% of people who smoked, 3% had left smoking, 2% were tobacco chewers and 86% did not smoke. Common manifestations associated with the deficiency included altered bowel habits (27%), peripheral neuropathy (18%), cognitive impairment (1%), dizziness (13%), heaviness sensation (1%), lethargy (3%), irritability (26%), generalized weakness (8%) and oral ulcerations (1%). Comorbid conditions associated with Vitamin B12 deficiency was Hypertension (22%), Hypothyroidism (7%), Diabetes (13%), Autoimmune disorder (5%), Migraine (1%), Hepatitis (1%), Coronary artery disease (9%) including Atrial fibrillation (2%), Rheumatic heart disease (2%), Neuropsychiatric manifestations (3%) including Depression (2%), Forgetfulness (1%), Joint involvement (8%), Worm infestation (7%), Malaria (6%), and Dyslipidemia (1%).

Conclusions: The deficiency was associated with a varied presentation – haematological, neurological, gastrointestinal, rheumatological, neurological, cardiological, endocrine, respiratory disorders and infections. It was more prevalent in the elderly and vegetarians but no significant correlation with socio-economic, educational status or gender was found. 2% people who were Vitamin B12 deficient were lactose intolerant. Vitamin B12 levels was lesser in people who did not take milk products and who consumed alcohol and had quit alcohol consumption. Vitamin B12 levels were less in smokers and past smokers. A significant association of combined deficiency of Vitamin B12 with Vitamin D3 was elicited. A good correlation of cognitive impairment, generalized weakness and reduced stamina was found with the deficiency. Lower Vitamin B12 levels in diabetics who were on metformin. Small sample size has been a limitation and all manifestations of Vitamin B12 deficiency found in literature review could not be elicited.

Key words: Vitamin B12, Deficiency, Spectrum, Correlation

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Introduction

Vitamin B12 is a water-soluble vitamin, required for protein, phospholipid and neurotransmitter metabolism and also for synthesis of S-adenosyl methionine [1]. The methionine synthase is essential for purine and pyrimidine synthesis. Accumulation of Methylmalonyl CoA is responsible for neurological effects. The human body can store Vitamin B12 for upto five years and its biochemical assessment is done by serum concentration [2,3]. Mostly, the deficiency is subclinical and it might take years to be apparent. In 1849, Vitamin B12 deficiency was first described and had a fatal outcome [2]. The deficiency is due to decreased or limited intake of animal foods or malabsorption which is common in elderly and secondary to gastric achlorhydria [2]. By 1926, it was found that dietary supplements e.g. liver is high in Vitamin B12 and slows the disease process [4]. The US Institute of Medicine recommends daily intake of 2.4 mcg of Vitamin B12 in adults older than 18 years of age [4, 5]. It also recommends adults over 51 years of age to have fortified foods and other supplements as there is a higher chance of gastritis [4].

Material and Methods

The study was conducted at the Max Super Specialty Hospital, Saket, New Delhi on 100 patients from May, 2014-May, 2015. This descriptive cross-sectional study was conducted to correlate the clinical spectrum of the deficiency including hematological, neurological and other complications with demographic data including age, gender, socio-economic data. Case was defined as a person with signs and symptoms of Vitamin B12 deficiency with serum Vitamin B12 <145 pg/ml and borderline if levels 145-180 pg/ml. The patients included adults more than 18 years excluding those who refused to participate in the study; who had taken Vitamin B12 supplementation (even one dose) in the past three months and with folate deficiency, from inpatient or outpatient department. Informed consent was taken and a detailed history, clinical examination and required investigations were done and incorporated in a structured format. Sample size was calculated at 95% confidence interval and 10 % precision taking prevalence of the deficiency as 35%. All statistical analysis were done using STATA 9.0 software.

Results

The results of our study are unique as the study correlates levels of vitamin B12 with clinical spectrum of the disease. There were 94% Indians, 2% Afghans, 1% British, 1% Iraqis, 1% Russian and 1% US American. Vitamin B12 deficiency was found to be more prevalent in Hindus compared to other religion (90% Hindus, 5% Muslims, 4% Christians). The deficiency was found in 77% people who took milk products and 21% who did not take milk at all. 2% of the people were lactose intolerant. But the mean value of serum Vitamin B12 levels was lesser in those who did not take milk at all (115.14+/-34.4 pg/ml) as compared to subjects who took milk (120.5+/-34.1 pg/ml) Table 1. The mean value of serum Vitamin B12 levels was lesser in subjects who took alcohol (97.94+/-38.1 pg/ml) to those who quit alcohol consumption (119+/-32.5 pg/ml) and in non-alcoholics (122.62+/-32.8 pg/ml). Table 2. The mean value of serum Vitamin B12 levels was lower in smokers and past smokers. Table 3. Vitamin B12 deficiency in this study was associated with altered bowel habits in 27%, irritability in 26%, peripheral neuropathy in 18%, dizziness in 13%, generalized weakness in 8%, lethargy in 3%, heaviness sensation in 1%, cognitive impairment in 1%, and oral ulcerations in 1% of the studied population with other comorbid conditions. Table 5.

Table 1: Relationship of S. Vitamin B12 Deficiency with Milk Products Intake (N=100)

Milk Products Intake	Mean	N	Std. Deviation	% of N
Lactose Intolerance	125.50	2	7.778	2.0%
No	115.14	21	34.404	21.0%
Yes	120.50	77	34.125	77.0%
Total	119.47	100	33.753	100.0%

Table 2: Relationship of S. Vitamin B12 Deficiency with Alcohol Intake (N=100)

ALCOHOL INTAKE 1. Yes 2. No 3. Occasional 4. Quit Alcohol Consumption	Mean	N	Std. Deviation	% of Total N
1.	97.94	14	38.174	14.0%
2.	122.62	76	32.838	76.0%
3.	127.38	8	24.389	8.0%
4.	119.00	2	32.527	2.0%
Total	119.47	100	33.753	100.0%

Table 3: Relationship of S. Vitamin B12 Deficiency with Smoking (N=100)

Smoker/Non-Smoker 1. Smoker 2. Non Smoker 3. Past Smoker 4. Tobacco	Mean	N	Std. Deviation	% of Total N
1.	113.33	9	30.000	9.0%
2.	120.46	86	35.020	86.0%
3.	108.00	3	15.875	3.0%
4.	122.00	2	2.828	2.0%
Total	119.47	100	33.753	100.0%

Table 4: Relationship of S. Vitamin B12 Deficiency with Vitamin D3 (N=50)

VITAMIN D3	Mean	N	Std. Deviation	% of Total N
< 30.00	119.82	44	32.632	88.0%
30.00+	109.50	6	25.509	12.0%
Total	118.58	50	31.817	100.0%

Table 5: Correlation of Vitamin B12 deficiency with diseases, signs and symptoms

Diseases, signs and symptoms	Mean	N	Std. Deviation	% of total N
Cognitive impairment	107.52	10	47.509	10%
Dizziness	110.69	13	21.857	13%
Generalised weakness, lethargy and reduced stamina	111.89	19	39.809	19%
Lethargy	98.00	3	70.150	3%
Peripheral neuropathy	120.12	18	39.850	18%
Generalised discomfort	108.63	8	18.094	8%
Oral ulceration	146.00	1		1%
Loss of weight	123.00	4	36.451	4%
Hyperpigmentation	173	1		1%
Hypertension	124.86	22	124.86+/-33.592	22%
Hypothyroidism	121.14	7	28.76	7%
Diabetes	115.31	13	36.529	13%

Vitamin D3 deficiency was found in 88% subjects who were Vitamin B12 deficient i.e. 44 of the 50 who were tested for Vitamin D3. This suggests a strong correlation with Vitamin D deficiency. The results are similar to those found in literature. Table 4.

Discussion

Vitamin B12 deficiency is one of the most common vitamin deficiencies. Aparicio-Ugarriza et al in 2014 published in Clinical, Chemistry and Laboratory Medicine review of the cut-off points for the diagnosis of Vitamin B12 deficiency in the general population (6) . For this study, a cut off value of 145pg/ml was taken for Vitamin B12 deficiency. Broad ranges of cut-off points for Vitamin B12 and its biomarkers were identified however there was inconsistency even in the available literature. Therefore, it is essential to establish different reference cut-offs.

This is a unique study as the spectrum of the deficiency in India has not been published so far although there are laboratory based studies showing a high prevalence of the deficiency. There was not enough literature with Indian data to analyze the symptomatology. This study gives an overview of the prevalence of the disease in India in a tertiary care set up.

The study does not provide too much information regarding demographical association (race, religion, socio-economic status) as it is not a true representation of the total population of India. According to literature, Vitamin B12 deficiency is more common in elderly (7). 2% of people above 80 years of age and 15% above 60 were Vitamin B12 deficient in this study. Therefore, it is recommended that older people should have fortified foods and supplements to meet their needs and requirements(8,9). People who did not take milk products at all were found to have lower levels of Vitamin B12 and it was more common in vegetarians (10). 2% subjects were lactose intolerant, 77% took milk products and 21% did not take any milk products at all. 14% of the people took alcohol, 8% were occasional drinkers and 2 % had left drinking and 76% of the people did not drink at all. 9% smoked, 3% had quit smoking, 2% were tobacco chewers and 86% did not smoke at all.

In literature, pregnant women were deficient in serum Vitamin B12 compared to non-pregnant females (11). Nothing significant was found in the child bearing age group as only one patient was enrolled in this study. A larger sample size or a study population would definitely give a better picture of the deficiency. The number of males (52%) and females (48%) with the deficiency was almost equal and there is no gender differentiation for the deficiency in this study.

An article published in Plos One of a large cross sectional survey on Vietnamese women studied overweight and micronutrient deficiency and found a positive correlation (12). Similar results were found in this study (BMI <23 in 30.4%, between 23-25 in 20.7% and >25 in 48.9%).

Review of literature supported the presentations of Vitamin B12 deficiency with the sensory and motor nerve function(13), atrophic gastritis (14), Diabetic Retinopathy(15), hormonal contraceptives and bone mineral density(16), Alcoholics (17) etc. Supportive

investigations such as methylmalonic acid and homocysteine to confirm the diagnosis of the etiology of the diseased deficiency state can diagnose the condition better.

A small sample size has been a limitation for this study. All the presentations found in the literature review could not be elicited in my study. Therefore, a larger sample size at multisite multi hospital would highlight various presentations of the deficiency. The study had more inpatients than outpatients for enrolment as it was easier to recruit admitted hospital patients. Mass screening of Vitamin B12 should be done to illicit the prevalence of Vitamin B12 deficiency including rural and urban populations. Food fortification programs in patients of cardiovascular disease (18), elderly and pregnant females should be introduced and incorporated to decrease the prevalence of the deficiency. Different studies quote different cut off values for Vitamin B12 deficiency therefore a standard value should be derived for the deficiency.

Conclusion

This descriptive cross sectional study is unique, describing the clinical spectrum of deficiency ranging from hematological, neurological, gastrointestinal, rheumatologic, neurological, cardiological, endocrine, respiratory disorders to association with infections in a tertiary care hospital. It was prevalent in the elderly. However, no significant correlation with socio-economic and educational status or gender was found in this study. The deficiency was associated in 2% lactose intolerant people and Vitamin B12 levels was lesser in people who did not consume milk products; in subjects who consumed alcohol, who had quit alcohol and in smokers and past smokers. There was a good correlation of cognitive impairment, generalized weakness and reduced stamina. Type 11 diabetics on Metformin showed lower Vitamin B12 levels. There was a good correlation of combined deficiency of Vitamin B12 and Vitamin D3. Mass screening of people with a larger sample size, multi-hospital, multi-center approach would give a better spectrum of manifestation including rural and urban population. Food fortification programs should be introduced and incorporated and a standard cut off value for serum vitamin B12 deficiency should be derived.

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Ethics: There is no ethical violation as it is based on voluntary anonymous interviews

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